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TITLE: Phase 2 Study of AZD2014, a Dual mTORC1/mTORC1 Inhibitor, for NF2 Patients with Progressive or Symptomatic Meningiomas

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14. ABSTRACT

Meningiomas are common in neurofibromatosis 2 (NF2) patients with a cumulative incidence of 80% by 70 years of age. Meningiomas that progress despite surgery and radiation are an important unmet medical need for these patients. To date, no chemotherapy has demonstrated efficacy against NF2-related meningiomas. Our laboratory studies have shown that treatment of primary meningioma cells with AZD2014, a mTORC1/mTORC2 inhibitor, leads to decreased cell viability/proliferation. Thus, we hypothesize that AZD2014 will be effective in treating symptomatic or progressive meningiomas in NF2 patients. In this single arm, non-comparative, phase II trial, 18 patients will be treated with AZD2014 for recurrent or progressive intracranial meningioma. AZD2014 will be administered on a repeating basis at a dose of 125 mg twice daily for two consecutive days out of every seven days (1 cycle = 28 days). Treatment will continue until disease progression or intolerable side effects. An MRI of the brain, with and without contrast, will be obtained every 12 weeks to assess for disease response or stability using volumetric measurements. In year 1, 14/18 subjects were enrolled on the study and accrual is expected to complete in year 2. Data analysis for efficacy and toxicity will begin around month 42 of the study.

15. SUBJECT TERMS					
Meningioma; mTORC; vistusertib; neurofibromatosis 2					
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INTRODUCTION

Neurofibromatosis 2 (NF2) is a neurogenetic tumor suppressor syndrome with a birth prevalence of 1 in 25,000 to 1 in 33,000. Patients with NF2 are at increased risk for multiple tumor types, including schwannomas, meningiomas, and ependymomas. Meningiomas are common in NF2 patients with a cumulative incidence of 80% by 70 years of age without a clear gender bias. Meningiomas that progress despite surgery and radiation are an important unmet medical need for these patients. To date, no chemotherapy has demonstrated efficacy against NF2-related meningiomas, and therefore, effective salvage therapies are greatly needed. Our laboratory studies have shown that treatment of primary meningioma cells with AZD2014, a mTORC1/mTORC2 inhibitor, leads to decreased cell viability/proliferation. Thus, we hypothesize that AZD2014 will be effective in treating symptomatic or progressive meningiomas in NF2 patients. In this single arm, non-comparative, phase II trial, 18 patients will be treated with AZD2014 for recurrent or progressive intracranial meningioma. AZD2014 will be administered on a repeating basis at a dose of 125 mg twice daily for two consecutive days out of every seven days (1 cycle = 28 days). Treatment will continue until disease progression or intolerable side effects. An MRI of the brain, with and without contrast, will be obtained every 12 weeks to assess for disease response or stability using volumetric measurements.

KEYWORDS

Neurofibromatosis 2; meningioma; mTOR; TORC1; TORC2

ACCOMPLISHMENTS

This section describes the key research accomplishments associated with each task outlined in the approved Statement of Work during the grant.

Major Task 1. Obtain institutional approval for proposed clinical trial (months 1-6)

In year 1, we obtained IRB approval at MGH and USAMRMC Human Research Protection Office (HRPO) to enroll subjects in the clinical trial. The following subtasks were completed during the first 4 months of the study.

	Projected Timeline (month)	**Actual Timeline (month)**
Refine eligibility criteria, exclusion criteria, screening protocol	1	1
Finalize consent form & human subjects protocol	1	1
SRC** protocol submission	1-3	1
IRB** protocol submission	1-3	1
Submit Investigational New Drug (IND) application to the U.S. Food and Drug Administration	4	1
Submit for Military 2nd level IRB** review (ORP/HRPO)	5	3
Local SRC/IRB approval	5	4
HRPO approval	6	4

All stated goals for Major Task 1 are complete.

Major Task 2. Enroll subjects in clinical trial (month 7-36)

In year 1, we projected that 4/18 subjects would be enrolled on the clinical trial. As of 5/30/2017, a total of 14/18 patients have been enrolled on the clinical trial. Thus, clinical trial enrollment is ahead of schedule. We hope to complete enrollment during year 2 of the study.

Major Task 3. Perform genetic and immunohistochemical analysis (months 7-36)

A second aim of the study is to perform molecular analyses of tumors and blood for correlation with response to AZD2014.

We have collected archival meningioma specimens in all 14 subjects enrolled on the study to date. In addition, blood samples from all 14 subjects are available and stored for analysis.

Once archival tumor specimens and blood specimens are available for all 18 subjects, we will perform genetic analyses on all available tumor tissue and blood for patients enrolled in this study by sequencing *NF2*, as well as performing immunohistochemical analyses of pS6 (as mTORC1 readout), pNDRG1, pAKT (as mTORC2 readout). This will enable analysis of drug response by a particular genetic mutation of *NF2*, mTORC1/mTORC2 activation status in meningiomas. We anticipate that this analysis will begin around month 24 of the study.

Major Task 4. Data analysis and presentation of results (months 12-48)

Interim analysis of subject accrual occurred at month 12. As noted above, 14/18 patients have been accrued during year 1. Our goal is to complete subject accrual during year 2 of the study.

Data analysis on the efficacy and toxicity of AZD2014 is scheduled to begin in month 42 of the study.

IMPACT

Nothing to report at this point in the study.

CHANGES/PROBLEMS

Nothing to report.

PRODUCTS

Nothing to report

PARTICIPANTS

Name	Scott Plotkin, MD, PhD
Project Role	Principal Investigator
Nearest person-month worked	2
Contribution to project	Dr. Plotkin serves a leadership role on this project and is coordinating the administrative and clinical aspects of the trial.
Funding support	N/A

Name	Vijaya Ramesh, PhD
Project Role	Co-Investigator
Nearest person-month worked	2
Contribution to project	Dr. Ramesh is the head of the research laboratory responsible for the correlative studies in this trial. She provides the laboratory infrastructure for genetic and immunohistochemical analysis of blood and tumor specimens.
Funding support	N/A

Name	Justin Jordan, MD, MPH
Project Role	Co-Investigator
Nearest person-month worked	1

Contribution to project	Dr. Jordan is a clinical specialist who has treated subjects on clinical trial, assisted with the administrative responsibilities of the study, and is helping to ensure that tissues are received in Dr. Ramesh's laboratory.
Funding support	N/A

Name	Alona Muzikansky, MA
Project Role	Statistician
Nearest person-month worked	1
Contribution to project	Ms. Muzikansky has provided statistical support for the clinical trial.
Funding support	N/A

Name	Nicola Gribbin, RN
Project Role	Research Nurse
Nearest person-month worked	1
Contribution to project	Ms. Gribbin has performed the duties of a research nurse in this study, helping with subject assessments, management of toxicity, and dispensing of AZD2014.
Funding support	N/A

Name	Annie Sposato
Project Role	Clinical research coordinator
Nearest person-month worked	1
Contribution to project	Ms. Sposato has coordinated the scheduling for subjects enrolled on the study.
Funding support	N/A

The following changes have occurred in the active support for both Drs. Plotkin and Ramesh: funding for the project entitled, "Applying systems biology to create tools and treatment paradigms for NF2-associated meningioma and vestibular schwannoma" has closed.

No other organizations were involved as partners.

SPECIAL REPORTING REQUIREMENTS

Not applicable

APPENDICES

None